Asian Journal of Medical Sciences 2(3): 141-145, 2010
ISSN: 2040-8773

Submitted Date: April 22, 2010 Accepted Date: May 14, 2010 Published Date: June 25, 2010

Glomerular Filtration Rate Assessment Using Creatinine Related Parameters for Healthy Adult Kenyan Population

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Abstract: The purpose of the study was to establish the reference ranges of measured creatinine clearance and estimated creatinine clearance for adult Kenyan population. A prospective study carried out in clinical chemistry laboratory of Kenyatta National Hospital involving 265 healthy individuals between 18-60 years. Reference ranges were constructed by using the parametric methods to estimate 2.5 and 97.5 percentiles of distribution as lower and upper reference limits. The glomerular filtration rate assessment of the adult healthy Kenyan population was carried out by investigating Serum Creatinine (SrCr), 24 h urine creatinine clearance (Mcrcl), estimated creatinine clearance (Ecrcl), Urine Creatinine (UCr) and Urine Volume (UV). Two hundred and sixty five voluntarily study subjects comprising of 106 male and 159 females were recruited in the study. Sex related reference values were established as follows: SrCr [male:68-128), female: 60-122] umol/l, Mcrcl [male:52-110), female: 50-92] ml/min, Ecrcl [male:54-118), female: 58-106] ml/min, UCr [male:3588-10,400, female:3262-9886] umol/l and UV [male:875-2301, female: 802-2092] ml/24 h. Same sex mean difference was found for the established reference ranges of Mcrcl and Ecrcl (male p = 0.021 and female p = 0.000). Decline rate in creatinine clearance in the ages under investigation were: male measured creatinine clearance (0.46 ml/min/year), male estimated creatinine clearance (0.29 ml/min), female measured creatinine clearance (0.39 ml/min/year) and female estimated creatinine clearance (0.2 ml/min). In conclusion, sex specific reference ranges for the assessment of glomerular filtration rate has been established. Age is an important factor in the interpretation of creatinine clearance of an individual. These reference ranges are different from those reported in literature, therefore each clinical chemistry laboratory should establish its own.

Key words: Adult kenyan, glomerular filtration rate, kenyatta national hospital, reference range

INTRODUCTION

Clearing of nitrogenous waste products from the blood stream is a key role of the kidney. This function is achieved through the filtration process that takes place in the glomerulus section of the kidney. The effectiveness and the ability of the kidney to clear the nitrogenuous waste products is measured through Glomerulus Filtration Rate (GFR) (Duarte *et al*., 1993). GFR can be determined by measuring any chemical that has a steady level in the blood and is freely filtered but neither reabsorbed nor secreted by the kidney. The knowledge of the kidney excretory function is useful in the diagnosis of renal impairments and in chemotherapy management (Koenig *et al*., 2002).

Several methods have been used in the determination of GFR eg inulin, hippuran, iohexol fluorescence, Creatinine Clearance (CrCl), serum creatinine, Blood Urea Nitrogen (BUN), urine microalbumin and serum cystatin C (Finney *et al*., 2000). Inulin, hippuran and iohexol are neither secreted nor absorbed by the kidney tubules. The clearance of these substances makes them better indicators of GFR, however they are impractical clearance tests for routine use. CrCl is a more widely used method in the evaluation of GFR (Lindegaard *et al*., 1991; Montgomery *et al*., 2000; Rossini *et al*., 2009).

In clinical management of patients, physicians rely on blood chemistry analytes for accurate diagnosis, proper treatment and follow-up of patients. Correct interpretation of the results from these analytes presupposes that the clinician and the laboratory medicine physician have good reference information. Published reference ranges in literature, do not represent adequately the specific population from which the patient comes from based on age, sex, genetics, diet, and altitude. In addition, reference ranges produced by reagent manufacturers are determined from analysis of blood samples of a few health workers who do not represent the general population. Reference information is often the weakest data provided by clinical laboratories even though such data is very useful for the correct and proper interpretation of laboratory results. IFCC therefore, recommends that each clinical chemistry

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laboratory establish its own reference range for biochemical parameters (IFCC, 1981; Ferre *et al*., 1999). There are no published reference ranges for creatinine clearance, which measures the glomelular filtration rate for Kenyan adult population. Clinical Chemistry Laboratory of Kenyatta National Hospital relies on reagent manufacturers' published reference ranges, which may not adequately represent Kenyan adult population. Objective of this study was therefore to establish reference ranges for measured creatinine clearance and estimated creatinine clearance for adult Kenyan population. The Kenyatta National Hospital Research and Ethical Committee approved the study (P342/11/2007).

MATERIALS AND METHODS

Study site: Nairobi Metropolitan Region of Kenya

Study period: April 2009-December 2009

Selection of study population: In the recruitment process, prospective study subjects were sensitized first. Sensitization was done through organized public lectures in Kenyatta National Hospital, medical colleges and universities within the Nairobi Metropolitan Region of Kenya. 265 individuals comprising of 159 females and 106 males between 18-60 years were recruited for the study. Sample size was determined according to Bartlett method (Bartlett *et al*., 2001). The inclusion/exclusion criteria were: Kenyan citizen, 18-60 years, not obese, not hypertensive, not pregnant, not involved in any excessive exercise, abstained from meat containing meals for three days prior to the test, not under any medication, not taking any oral contraceptives (female subjects), none alcohol and tobacco users. Those who met the inclusion/exclusion criteria were requested to give consent, to be involved in the study. Age of study participant was in particular noted on the questioner. This parameter was used for the estimation of creatinine clearance using Cockcroft and Gault (1976) formular.

Specimen collection and analysis: A pre-prepared 5L urine container with 10 mL of concentrated hydrochloric acid was given to each consenting study subject. Instructions were given to discard the first morning urine voided and thereafter to collect all the urine voided for the next 24 h. The method of urine collection was to urinate in a clean container and then transferring the urine carefully into the 5 L pre-prepared urine container. Urine Volume (UV) was measured using a clean 2 L measuring cylinder. Approximately 1 mL of the collected urine was reserved for creatinine analysis. 2 mL of blood was drawn from the study subject within the urine collection interval. Serum was separated by centrifugation at 3000 g. Serum Creatinine (SCr) and Urine Creatinine (UCr) were determined by modified Jaffe reaction method using Olympus 640 AU autoanalyzer. Assayed multisera normal was used for the quality control of analytical work during study period. The following formulas were used for the determination of measured creatinine clearance (Mcrcl) and estimated creatinine clearance (Ecrcl) respectively:

$$Mcrcl = \frac{UV(mL) \times UCr(\mu mol/L)/1440sec}{SCr(\mu mol/L)}$$

$$Ecrcl = \frac{(140-age) \times weight\ (kg) \times constant\ (male = 1.23,\ female = 1.04)}{SCr\ (\mu mol/L)}$$

The weight of each study subject was taken by weigh using a weigh balance

RESULTS

The female study participants had a mean age and weight of 34.5 years and 69.5 kg respectively. On the other hand the male study participants had a mean age and height of 33.1 years and 64.1 kg respectively. Mean difference for all the studied parameters were statistically significant for both sexes with p-value less than 0.05 as shown in Table 1. Sex related reference ranges for serum creatinine, measured creatinine clearance, estimated creatinine clearance, urine volume and urine creatinine were constructed using mean±1.96SD.

Same sex mean difference was found to be statistically significant for established Mcrcl and Ecrcl for both male ($p = 0.021$) and female ($p = 0.001$) as shown in Table 2.

Study participants were categorized in four groups ie group 1(18-28), group 2(29-39), group 3(40-50) and group 4(51-61) years, for each gender and the mean standard deviation of each group was determined as shown in Table 3. A relationship between age and creatinine clearance was established where creatinine clearance decreases as age advances in both sex.

Creatinine clearance significantly ($p = 0.001$) declined at a rate of 0.46 ml/min per year for males from ages 18 to 60 years for measured creatinine clearance. Estimated creatinine clearance of the same male study participants had a significant ($p = 0.001$) decline of 0.29 ml/min/year. On the other hand, creatinine clearance significantly ($p = 0.001$) declined at a rate of 0.39 ml/min/year for females from ages 18 to 60 years for measured creatinine clearance. Estimated creatinine clearance of the same female study participants had a significant ($p = 0.001$) decline of 0.2 ml/min/year.

DISCUSSION

Estimation of Glomerular Filtration Rate (GFR) is crucial for the diagnosis, evalution and management of

Table 1:Sex related reference ranges for serum creatinine, measured creatinine clearance, estimated creatinine clearance, urine volume and urine creatinine

Parameter (unit)	Sex	N	Mean±SD	Rr	p-value
SCr (µmol/L)	M	106	97.9±15.2	68-128	0.001
	F	159	90.5±15.7	60-122	
Mcrcl (ml/min)	M	106	81.3±14.8	52-110	0.001
	F	159	71.6±10.8	50-92	
Ecrcl(ml/min)	M	106	85.6±16.4	54-118	0.001
	F	159	81.7±12.4	58-106	
UV (ml)	M	106	1588±364	875-2301	0.001
	F	159	1447±329	802-2092	
UCr (µmol/L)	M	106	6994±1738	3588-10,400	0.001
	F	159	6574±1690	3262-9886	

Results are expressed as mean ± standard deviation (SD), The reference range (Rr) for each analyte was calculated as the minimum and maximum value of 95% of the study subjects using the formula mean (X) ± 1.96 standard deviation (SD), N = Number of study subjects

Table 2: Same sex differences for Mcrcl and Ecrcl

Parameter(unit)	Sex	N	Mean±SD	p-value
Mcrcl (ml/min)	M	106	81.3 ± 14.83	0.021
Ecrcl (ml/min)	M	106	85.6 ± 16.4	
Mcrcl (ml/min)	F	159	71.6 ± 10.75	0.001
Ecrcl (ml/min)	F	159	81.7 ± 12.4	

N = Number of study subjects, Mcrcl = Measured creatinine clearance, Ecrcl = Estimated creatinine clearance

Table 3: Relationship between age and creatinine clearance

Age group (years)	Sex	N	Mcrcl (ml/min)	Ecrcl (ml/min)
18-28	M	38	89.1±14.6	91.3±19.6
	F	54	77.1±9.9	81.1±11.8
29-39	M	40	80.0±12.4	85.5±13.9
	F	47	72.9±9.8	79.9±10.7
40-50	M	23	77.2±9.2	80.8±10.6
	F	49	66.7±9.3	76.2±11.1
51-61	M	5	69.8±7.0	78.8±11.4
	F	9	60.9±8.7	72.7±12.5

N = Number of study subjects, Mcrcl = Measured creatinine clearance, Ecrcl = Estimated creatinine clearance

renal pathological disorders. Reference values for measured creatinine clearance, estimated creatinine clearance, serum creatinine, urine volume and urine creatinine were determined in 265 healthy Kenyan adults ages 18-65 years. These study participants comprised of 106(40%) males and 159(60%) females. Since the accuracy of measured creatinine clearance depends on the accuracy of the urine collection, intensive sensitization exercise was carried out on the study subjects prior to the commencement of urine specimen collection thus keeping variability in creatinine excretion due to incomplete urine collection to a minimum. In addition, study subjects were not allowed to exercise during or prior to the study thus eliminating potential variability of creatinine due to this factor (Lori *et al*., 1994). The effect of cooked meat (Jacobsen *et al*., 1979; Mayersohn *et al*., 1983) on creatinine clearance was controlled in this study as well, with no intake of meat by the subjects during or three days prior to the study period.

Effect of body muscle mass on serum creatinine levels, where males generally have a higher muscle mass than females (Heymsfield *et al*., 1993) was expressed in this study. Males had higher serum creatinine levels (97.9±15.2) than the female counterparts (90.5±15.7) and the mean difference was significant (p = 0.001). It is therefore evident that males have a higher body muscle mass than females and this effect has been expressed in related studies carried out elsewhere ((Lori *et al*., 1994)). Sex related serum creatinine levels of the current study population are similar to those obtained in an earlier studied Kenyan adult population (Waithaka *et al*., 2009).

Determination of glomerular filtration rate for the studied Kenyan population was achieved through two commonly used methods ie measured creatinine clearance and estimated creatinine clearance. The achievement of proper urine collection played a major key role in the establishment of reference values of measured creatinine clearance since urine volume and urine creatinine are integral part of the applied formular. The current study produced sex-related reference values for both urine volume and urine creatinine whereby the male's value (1588±364) was higher than the female's (1447±329) and the mean difference was statistically significant (p = 0.001) Significant gender difference (p = 0.001) was found in measured creatinine clearance whereby males (81.3±14.83) value was higher than that of the females (71.6±10.75). Similar gender difference in measured creatinine clearance was found in other population studied elsewhere (Finney *et al*., 2000).

It is useful and quite convenient to determine creatinine clearance by estimation without the need for urine collections. Estimated creatinine clearance was

carried using the Cockcroft and Gault (1976) formular, which employ serum creatinine levels, age (years) and weight (kg) to predict the creatinine clearance of a study participant. The current study came up with sex related estimated creatinine clearance reference values with the males (85.6±16.4) having a higher value than the females (81.7±12.4). Gender differences in estimated creatinine clearance could be attributed to body muscle mass difference between male and female. Comparatively, generated estimated creatinine clearance values are higher (male: 85.6±16, female: 81.7±12.4) than the measured creatinine clearance values (male: 81.3±14, female: 71.6±10.75) In addition, the difference between these two methods for creatinine clearance analysis is significant in both sex (male: $p = 0.021$, female: $p = 0.001$).

Current study has shown a relationship between age and creatinine clearance. Creatinine clearance declines as age progress but at different rates depending on the sex of an individual and the method used for analysis. Decline rate is higher in males than in females for measured creatinine clearance whilst the decline rate is almost the same for male and female in estimated creatinine clearance. A similar study carried out on older women from ages 40 to 95 years was in agreement with the current study in that as age progress creatinine clearance declines (Lori *et al.*, 1994). This fall of creatinine clearance with age across the gender could be attributed to subclinical pathology (Fliser *et al.*, 1997).

CONCLUSION

This is the first study to determine the GFR for the Kenyan population using measured and estimated creatinine clearance methods of analysis. It is evident from this study that male and female have different reference ranges for either the measured or estimated creatinine clearance. Considering the two methods of creatinine clearance analysis, measured creatinine clearance produced lower values than estimated creatinine clearance. This factor is worth considering whenever the generated creatinine clearance reference ranges are used in the interpretation of creatinine clearance laboratory results. There was a progressive decline of creatinine clearance with age in this study therefore age of an individual should be considered whenever references from the study are to be made. The study recommends the usage of reference ranges reported in this study, thus making it independent from what has been quoted in literature. There is great need to establish creatinine clearance reference ranges for the individuals whose age group is outside the ones considered in this study. The findings of this study serve as an avenue opener for similar studies to be carried out in other geographical regions.

RECOMMENDATION

Due to the differences in references ranges from different geographical locations, the authors recommends the usage of the established reference ranges of the studied parameters in the Kenyan health institutions. The authors recommend similar studies to be carried to establish reference ranges of the studied parameters for the other age groups not included in this current study.

ACKNOWLEDGMENT

The authors would like to thank the study participants for their cooperation in the conduct of this study. The analytical equipments were provided by Kenyatta National Hospital (KNH). We thank the Director of KNH and the Head of Department of Laboratory Medicine KNH, for their support. We gratefully acknowledge the contribution made by Flambart Holdings and Chem Labs for the provision of reagents to carry out the analytical work. We appreciate the excellent technical assistance provided by Lucy Nyokabi Kimani, Joyce Muthoni Gachoki, Jackan Mwanjala Moshe of Jomo Kenyatta University of Agriculture and Technology and Justus Oyemba Walukale of Kenyatta National Hospital. We also appreciate the professional data handling and entry done by Irene Wanjiru Kaguru.

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